M-I-(2) Non-technical abstract

The proposed phase 1 study entitled: "Direct Administration of a Replication Deficient Adenovirus Vector (Ad_{GV}VEGF121.10) Containing the $VEGF_{121}$ cDNA to the Ischemic Lower Limb of Individuals with Peripheral Vascular Disease" utilizes the identical Ad_{GV}VEGF121.10 vector that is approved by the Food and Drug Administration (FDA) for the treatment of coronary artery disease under RAC#9711-211, "Direct Administration of a Replication Deficient Adenovirus Vector (Ad_{GV}VEGF121.10) Containing the $VEGF_{121}$ cDNA to the Ischemic Myocardium of Individuals with Life Threatening Coronary Artery Disease" that was discussed by the RAC at the December 9, 1997 meeting.

Ad_{GV}VEGF121.10, is an FDA approved biologic product for the administration to the myocardium (heart) of individuals with coronary artery disease, a condition associated with narrowing of the arteries of the heart and reduced blood flow to specific areas of the heart. In the proposed clinical protocol, Ad_{GV}VEGF121.10 is intended to treat patients with peripheral vascular disease, a condition associated with atherosclerosis (narrowing of the arteries) of the lower extremities, and reduced blood flow. This study uses an experimental drug which is referred to as a vector. The vector, called Ad_{GV}VEGF121.10, is a laboratory altered virus that can infect cells in the body like a "cold" virus, but unlike a "cold" virus it cannot reproduce itself and cause a cold. The Ad_{GV}VEGF121.10 vector contains a gene called VEGF (Vascular Endothelial Growth Factor). The VEGF gene is normally found in the human body and stimulates growth of blood vessels. The concept of administering this vector to the lower limb in an area of reduced blood flow is that the vector carries the VEGF gene into cells of the lower limb and these cells produce VEGF proteins that cause new blood vessels to grow. New blood vessels will then increase blood flow to the areas of the lower limb experiencing reduced blood flow. Because the VEGF protein is from human genes, the body will not recognize it as "foreign" and will not produce an immune response (the body's defense).

The proposed clinical protocol is a randomized double blinded, dose-escalating study involving a total of 40 individuals that is divided into 2 parts: A and B. Part A is a dose escalating safety study of 20 individuals with lower limb claudication, (pain upon walking) where no surgery is contemplated for at least >6 months. Part B will include 20 individuals that have limb threatening ischemia (reduced blood flow) where surgery is not possible. Two types of controls are built into Parts A and B of the study. First, each individual will serve as their own control before and after therapy. Second, in each dose group of n=4, 1 of the 4 individuals (in a double blind, randomized basis) will receive the vector diluent, (a sugar salt solution) and 3 of 4 individuals will receive the Ad_{GV}VEGF121.10 vector. The total doses for Parts A and B will range from $4x10^8$-$4x10^{10}$ particle units. All groups will be assessed with a variety of safety and efficacy parameters relevant to peripheral vascular disease. The following objectives will be met: (1) To determine the dose-dependent safety of direct administration of the vector Ad_{GV}VEGF121.10 to the ischemic lower limb; and (2) To demonstrate whether direct administration of Ad_{GV}VEGF121.10 to the lower limb will induce growth of collateral blood vessels, improve blood flow, and improve function in the region of ischemia.